1,077,689

PATENT SPECIFICATION

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The inventors of this invention in the sense of being the devisers thereof within the meaning of Section 16 of the Patents Act, 1949 are:—FELIX G. BERGMANN of 3 Disraeli Street, Jerusalem, ZOHAN NEIMAN of Shikun Hamekasher II, Jerusalem, and MORDECHAI KLEINER of 95 Rothschild Street, Petach-Tikva, all Israeli citizens.

COMPLETE SPECIFICATION

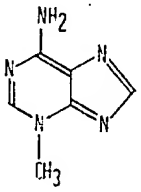
Derivatives of 3-Methylpurine and methods of preparing the same

We, YISSUM RESEARCH DEVELOPMENT COMPANY, of Administration Building, The Hebrew University, Jerusalem, Israel, a Company registered under the Laws of the State of Israel, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

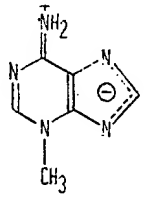
This invention relates to new derivatives of 3-methylpurine and to methods of preparing such derivatives.

Substituted purines containing a substituent methyl group at the 3-position are of interest because the peculiar quinonoid form of the imidazole ring in conjugation with double bonds in the pyrimidine ring would be expected to cause increased reactivity.

It is known that such 3-methylpurines are stabilised by substituents at the 6-position. Thus, for example, in 3-methyladenine, which has been shown to possess the structure:



electron donation by the substituent at the 6-position is believed to produce a switterionic form:



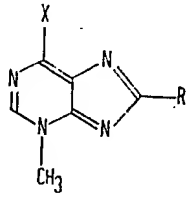
in which stabilisation is presumably achieved by replacement of the original *o*-quinonoid pyrimidine ring by a *p*-quinonoid form.

It would be expected, therefore, that proper substitution in other positions, e.g. by the introduction of a resonating aromatic group in the 8-position, would also stabilise 3-methylpurines.

It is an object of the present invention to provide a series of new derivatives of 3-methylpurine which are stabilised by substitution in the 6-position and/or 8-position.

It is a further object of the invention to provide methods of preparing these new derivatives.

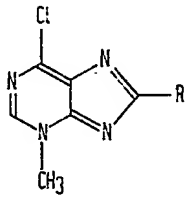
According to the invention, there are provided new 3-methylpurine derivatives of the general formula;



[*Price 4s. 6d.*]

where R is hydrogen and X is chlorine or a methoxy group; or where R is an aromatic group or a heterocyclic group of aromatic character and X is hydrogen, or chlorine, or a methoxy group, or a methylamino group, or a dimethylamino group.

The 6 - chloro - 3 - methylpurines of the formula:



where R is hydrogen or an aromatic group or heterocyclic group of aromatic character, for example, 6 - chloro - 3 - methylpurine or 6 - chloro - 3 - methyl - 8 - phenylpurine, have been found to be markedly reactive and suitable as starting materials for other 3-methylpurines substituted at the 6-position. These 6-chloro derivatives can be prepared by reacting the corresponding 3 - methyl - 6-methylthiopurines with gaseous chlorine in methanol solution at a temperature of below −3°C.

The chlorine atom in these 6 - chloro - 3-methylpurines is readily replaced by other groups. Thus 6 - chloro - 3 - methylpurine itself readily reacts with methanol to form 6-methoxy - 3 - methylpurine, even at room temperature, and with ethanol to form 6-ethoxy - 3 - methylpurine. With dimethylamine, 6 - chloro - 3 - methylpurine forms at room temperature the corresponding adenine derivative, 6 - dimethylamino - 3 - methylpurine. When the 6 - chloro - 3 - methylpurine is heated with sodium acetate in aqueous acetic acid, the corresponding 3-methylhypoxanthine is formed. The 3-methylhypoxanthines can also be prepared by reacting the corresponding 6 - methoxy - 3-methylpurine with aqueous hydrochloric acid.

6 - Chloro - 3 - methylpurine is relatively stable in the form of its hydrochloride. The free base can be isolated by cautious neutralisation of its hydrochloride with ammonia, but has been found to be considerably less stable. In solid form the free base darkened within a few days, even when the crystals were kept in the cold in a vacuum desiccator protected from light. In aqueous solution, it decomposed rapidly to 3 - methylhypoxanthine, especially in the presence of alkali.

In a similar manner, 6 - chloro - 3-methyl - 8 - phenylpurine can served as a starting material for the preparation of other corresponding purine derivatives. Thus it will react with ammonium sulphide at room temperature to give a quantitative yield of 6-thiono - 3 - methyl - 8 - phenylpurine. With methyl- and dimethylamine, it forms the corresponding adenines, 6 - methylamino - 3-methyl - 8 - phenylpurine and 6 - dimethylamino - 3 - methyl - 8 - phenylpurine respectively under mild conditions. Hydrolysis of 6-chloro - 3 - methyl - 8 - phenylpurine in acetate buffer solution gives 3 - methyl - 8-phenylhypoxanthine in nearly quantitative yield. Hydrogen chloride in absolute methanol converted 6 - chloro - 3 - methyl - 8 - phenylpurine into 6 - methoxy - 3 - methyl - 8-phenylpurine which in turn could be hydrolysed to 3 - methyl - 8 - phenyl hypoxanthine.

3 - Methyl - 8 - phenylpurine itself can be prepared by the desulphuration of 3-methyl - 6 - methylthio - 8 - phenylpurine in aqueous isopropanol using Raney nickel and is stable as the picrate.

The analogous compound 3 - methyl - 8-(3′ - pyridyl)purine can be prepared by the desulphuration of 2,6 - dithio - 3 - methyl-8 - (3′ - pyridyl)purine in dimethylformamide and aqueous ammonia using Raney nickel. The introduction of the 8-pyridyl substituent strongly increases the stability of the compound and 3 - methyl - 8 - (3′ - pyridyl)-purine can be crystallised as the free base. Other 3-methylpurines of the invention wherein R is aromatic or heterocyclic and X is halogen may be prepared in similar manner. The methylamino and dimethylamino derivatives of the 3-methylpurines can also be prepared by reacting the corresponding 3-methyl-6-methylthiopurines with monomethylamine and dimethylamine respectively.

The invention is illustrated by the following Examples. The purity of all compounds referred to in the Examples was checked by measurement of their absorbance and by paper chromatography. The chromatograms were developed on Whatman (Trade Mark) No. 1 paper by the descending method, using one or more of the following solvents:—

A — 95% by volume ethanol: dimethylformamide: water = 60:20:20 v/v;

B — *n*-butanol: water: acetic acid = 60:25:15 v/v;

C — propane-2-ol: dimethylformamide: 25% by weight ammonia = 65:25:10 v/v;

D — 95% ethtnol: water: acetic acid = 85:10:5 v/v.

Spots were located by their fluorescence under a Mineralight ultraviolet lamp ($\lambda \sim$ 255 mμ). UV spectra were determined with a Beckman (Trade Mark) DU spectrophotometer.

EXAMPLE 1.

Preparation of 6-Chloro-3-methylpurine

3 - Methyl - 6 - methylthiopurine (2g) was added in portions to a vigorously stirred, saturated solution of chlorine in absolute

methanol (25 ml), while care was taken to keep the temperature below −3°C, and to exclude all traces of moisture. After the addition was completed, chlorine gas was bubbled through the solution at −3°C for a further 10 minutes. The white precipitate was at once collected on a filter, washed with a little cold anhydrous benzene and transferred to a vacuum dessicator. Yield: 1g (60%). For purification, the product was dissolved in cold acetic acid and caused to crystallise by addition of excess of cold dioxane. White needles, representing the hydrochloride of 6-chloro-3-methylpurine were obtained; the compound darkens upon heating above 200°C, but does not melt even at 300°C. (Found: C, 36.0; 36.3; H, 2.9; 3.3; N, 27.0; Cl, 33.7; 33.7. $C_6H_5N_4Cl.HCl$ requires: C, 35.1; H, 2.9; N, 27.3; Cl, 34.6.)

The free base was prepared by dissolving the hydrochloride in ice-cold water and neutralisation with conc. ammonia, taking care to keep the temperature below +4°C. The precipitate was filtered off at once, dried in a desiccator in the dark and recrystallised from dioxane-benzene; long needles of m.p. 91—92°C (bath preheated to 80°) were obtained. (Found: C, 42.2; H, 3.6; N, 33.0; Cl, 20.9. $C_6H_5N_4Cl$ requires: C, 42.7; H, 3.0; N, 33.2; Cl, 21.1.)

EXAMPLE 2

Preparation of 6-Methoxy-3-methylpurine

A solution of 6 - chloro - 3 - methylpurine hydrochloride (3g) in absolute methanol (50 ml) was left at room temperature overnight. The solvent was removed in vacuo and the residue, representing the hydrochloride of 6-methoxy-3-methylpurine, dissolved in water. Upon adjustment of the pH to 10 by addition of 1H—NaOH, a white precipitate was formed, which was removed at once and recrystallised from water; needles of m.p. 162—163°C were obtained; pK=5.7. Yield: 1.5g (51%). (Found: C, 41.9; H, 6.0; N, 28.1. $C_7H_8N_4O.2H_2O$ requires: C,42.0; H, 6.0; N, 28.0%.)

The picrate of 6 - methoxy - 3 - methylpurine crystallised from aqueous acetone in yellow prisms, m.p. 196—198°C. (Found: C, 39.9; H, 3.0; N, 25.3. $C_{13}H_{11}N_7O_8$ requires: C, 39.7; H, 2.8; N, 24.9%.)

A solution of 6-methoxy-3-methylpurine (10 mg) in 5N—HCl (5 ml) was left at room temperature for 12 hours. The solution was concentrated in vacuo and then subjected to paper chromatography. Development with solvent B revealed the presence of a single spot with $R_F=0.35$ and λ_{max} (pH 8.0)=264 mμ identical with the values reported for 3-methylhypoxanthine (G. B. Elion, J. Org. Chem. 1964, *27* 2478).

EXAMPLE 3

Preparation of 6-Dimethylamino-3-methylpurine

6 - Chloro-3 - methylpurine hydrochloride (0.5g) was dissolved at room temperature in ethanol, containing 25% dimethylamine (20 ml.). A yellow colour appeared at once. After standing for 12 hours at room temperature, the solvent was removed in vacuo, the oily residue triturated with ethanol and again dried in vacuo, until the product (6-dimethylamino-3-methylpurine) was obtained as yellowish powder. The product was then converted into its picrate. Plates from acetic acid-dioxane, m.p. 190°C were obtained. R_F in solvent A, 0.67; in solvent C, 0.79; violet fluorescence; λ_{max} (pH 1) = 289.6 mμ. (Pal and Horton, J. Chem. Soc. 1964, 400).

EXAMPLE 4

Preparation of 3-Methyl-8-phenylpurine

A suspension of 3-methyl-6-methylthio-8-phenylpurine (5g) prepared according to our co-pending application No. 55412/65 in 50% aqueous isopropanol (150 ml) was refluxed in the presence of Raney nickel (30 g) for 5 hr. The catalyst was filtered off and the solution brought to dryness. The residual syrup showed λ_{max} = 226 and 317 mμ, but could not be induced to crystallise. When left in contact with the air, it darkened quickly. It was therefore converted into the picrate, which was recrystallised once from 70% aqueous isopropanol and twice from water. Yellow needles which darken at 180°C and decompose at about 210°C were obtained. Yield: 1g (12%). (Found: C, 49.5; H, 3.3; N, 22.65%. $C_{18}H_{13}N_7O_7$ requires 49.2; H, 3.0; N, 22.3.)

EXAMPLE 5

Preparation of 6-Chloro-3-methyl-8-phenylpurine

Absolute methanol (70 ml) was saturated with chlorine gas at 0°C. Under stirring, 3 - methyl - 6 - methylthio - 8 - phenylpurine (4g) was added in small portions, care being taken to keep the temperature at —4°C. Introduction of chlorine was then continued for 20 minutes. The white precipitate which had formed, was filtered off rapidly, washed with a small amount of dry, ice-cold benzene and transferred to a vacuum desiccator. The dry hydrochloride of 6 - chloro - 3 - methyl - 8-phenylpurine is easily soluble in water, has no definite m.p., and upon addition of silver nitrate gives at once a precipitate of silver chloride. Yield: 3g (69%). The free base was obtained by dissolving the hydrochloride (1g) in a minimum of cold water and adjusting the pH to 9 by cautious addition of conc. ammonia, while the temperature was kept near 0°C. The white precipitate was filtered off rapidly and dissolved in cold dioxane. After addition of cold benzene, 6 - chloro - 3-methyl - 8 - phenylpurine crystallised in needles of m.p. 225—227°C. Yield: 0.5g (73%). λ_{max} (pH 8.0) 234, 321 mμ; log ε_{max} 3.64, 3.86; R_F (solvent A) 0.82, (solvent C) 0.88; light blue fluorescence. (Found: C, 59.0; H, 3.7; N, 23.05. $C_{12}H_9N_4Cl$ requires: C, 58.9; H, 3.7; N, 22.9%.)

EXAMPLE 6

Preparation of 3-Methyl-8-phenyl-hypoxanthine

A solution of 6 - chloro - 3 - methyl - 8-phenylpurine hydrochloride (6g) and sodium acetate (6g) in 40% acetic acid (100 ml) was refluxed for 30 minutes. The yellow solution was decolorised with charcoal and cooled. From dilute acetic acid needles of dec. p. 300°C. Yield: 3.5g (72%). (Found: C, 63.3; H, 4.8; N, 24.6. $C_{12}H_{10}N_4O$ requires C, 63.7; H, 4.4; N, 24.8%). The carbonyl stretching frequency in the infrared spectrum (K Br discs) was found at 1650 cm^{-1}, similar to the value reported by Brown and Mason (Chem. Soc. 1957, p. 682) for 3-methylhypoxanthine.

In order to confirm that the compound obtained as above was 3 - methyl - 8 - phenyl-hypoxanthine, it was also prepared in an unequivocal way by the condensation of 4,5-diamino - 6 - hydroxy - 3 - methylpyrimidine with benzamidine hydrochloride, according to the general method of Bergmann and Tamari (Chem. Soc. 1961, p. 4468).

An intimate mixture of 4,5 - diamino - 6-hydroxy - 3 - methylpyrimidine (3g), benzamidine hydrochloride (12g) and sodium acetate (3g) was heated first to 180°C. The molten mass was then kept at 165°C. for 45 minutes. The cake was dissolved in hot 10% by volume acetic acid (150 ml), the solution decolourised with charcoal and filtered. White needles, decomposing at 300°C were obtained. Yield: 1.8g (36%). The product was identical in all respects with the 3 - methyl - 8 - phenyl-hypoxanthine prepared as described above.

EXAMPLE 7

Preparation of 6-Thiono-3-methyl-8-phenylpurine

To a cooled solution of hydrogen sulfide in conc. aqueous ammonia (30 ml) was added an aqueous solution of the hydrochloride of 6 - chloro - 3 - methyl - 8 - phenylpurine (2g). A yellow precipitate appeared at once. After hydrogen sulfide had been bubbled through for an additional 10 minutes, the precipitate was filtered off. From dilute acetic acid yellow microcrystalline aggregates, dec. p. 280—285°C were obtained. Yield: quantitative. (See, our co-pending application No. 55412/65).

EXAMPLE 8

Preparation of 6-Methylamino-3-methyl-8-phenylpurine

The hydrochloride of 6 - chloro - 3-methyl - 8 - phenylpurine (2g) was dissolved in 30% by weight aqueous methylamine (50 ml) and left at room temperature overnight. The mixture was then cooled to −10°C, the solid filtered off and recrystallised from dilute methanol. Plates of m.p. 190—192°C were obtained. Yield: 1g (51%); λ_{max} (pH 8.0) 236; 323 mμ; log ϵ_{max} 4.22; 4.37; R_F (solvent A) 0.89, (solvent C) 0.80; light blue fluorescence. (Found C, 64.7; H, 5.6; N, 29.4. $C_{13}H_{13}N_5$ requires: C, 65.3; H, 5.4; N, 29.3.)

EXAMPLE 9

Preparation of 6-Dimethylamino-3-methyl-8-phenylpurine

3 - Methyl - 6 - methylthio - 8 - phenylpurine (1g), dissolved in DMF (2 ml), was added to a solution of dimethylamine (2g) in 30 ml of 60% by volume aqueous ethanol. The mixture was heated on a water bath for 2 hours and then brought to dryness in vacuo. The residue formed a crystalline picrate. From acetonitrile-dioxane yellow prisms of m.p. 230—232°C were obtained. λ_{max} (pH 1.0) 238, 318mμ R_F (solvent B) 0.64, (solvent D) 0.67; grey fluorescence. (Found: C, 50.2; H, 4.2; N, 23.5. $C_{20}H_{18}N_8O_7$ requires: C, 49.8; H, 4.2; N, 23.2%.)

EXAMPLE 10

Preparation of 6-Methoxy-3-methyl-8-phenylpurine

6 - Chloro - 3 - methyl - 8 - phenylpurine hydrochloride (2g) was suspended in methanol (70 ml), which had been saturated with hydrogen chloride at +5°C. After 1.5 hours reflux, the solvent was distilled off, the residue dissolved in water and the pH adjusted to 10 by cautious addition of 1N—NaOH under cooling. The precipitate was filtered at once and recrystallised from dil. dioxane. Colorless needles of m.p. 174—176°C were obtained. Yield: 1g (56%). λ_{max} (pH 8.0) 310 mμ; log ϵ_{max} 4.43; R_F (solvent A) 0.82; white-blue fluorescence. (Found: C, 62.9; H, 5.3; N, 22.65. $C_{13}H_{12}N_4O$. 0.5 H_2O requires: C, 62.6; H, 5.2; N, 22.5%.)

The picrate crystallised from dilute ethanol in yellow prisms, m.p. 268—270°C. (Found: C, 48.65; H, 3.6; N, 21.15. $C_{19}H_{15}N_7O_8$ requires: C, 48.6; H, 3.2; N, 20.9%.)

EXAMPLE 11

Preparation of 3-Methyl-8-phenyl-hypoxanthine

A suspension of 6 - methoxy - 3 - methyl-8 - phenylpurine (100 mg) in 6N—HCl (20 ml) was refluxed for ¾ hour. It was converted quantitatively into 3 - methyl - 8 - phenyl-hypoxanthine, identical with the compound described in Example 6.

EXAMPLE 12

Preparation of 3-Methyl-8-(3'-pyridyl)-purine

(a) Preparation of 3 - methyl - 8 - (3'-pyridyl) - 2 - thioxanthine

An intimate mixture of 4,5 - diamino - 3-methyl - 2 - thiouracil, (prepared by the method of Bergmann, *et al.*, J. Org. Chem. 1961, *26*, 1504), (17.2g), nicotinamidine hydrochloride (prepared by the method of Schaefer and Peters, J. Org. Chem. 1961, *26*, 412), (31.3g) and anhydrous sodium acetate (16.4g) was kept for 20 minutes in a bath of 220°C. The cake was pulverised and dissolved in 5% by weight aqueous sodium carbonate (1 litre). The hot solution was decolorised with charcoal, filtered and kept overnight in the cold

room. The sodium salt of the thioxanthine was removed by filtration and redissolved in boiling water (800 ml.). The hot solution was neutralised with solid ammonium chloride and then acidulated by addition of a few drops of acetic acid. Yield: 18.5g (71%). Crystallisation from DMF: water = 2:1 gave pale yellow needles of dec. p. 310°C. λ_{max} (pH 8) 239 and 327 mμ; log ϵ_{max} 3.65 and 3.80, resp. R_F 0.45 (solvent A), 0.61 (B); grey-violet fluorescence. (Found: C, 51.0; H, 3.4; N, 27.4; S, 12.4%. $C_{11}H_9N_5OS$ requires: C, 51.0; H, 3.5; N, 27.0; S, 12.4.)

(b) preparation of 2,6 - dithio - 3 - methyl-8 - (3' - pyridyl)xanthine

A suspension of the foregoing substance (16 g) and phosphorus pentasulphide (64g) in pyridine (800 ml) was stirred and refluxed for 2 hours. The mixture became homogeneous after a short while and slowly turned red. The solvent was removed in vacuo and the residue decomposed at room temperature with water (200 ml.) the insoluble part was filtered off and dissolved in 1N—NaOH. After decolorisation with charcoal, the solution was neutralised with ammonium chloride. From DMF yellow prisms were obtained, dec. p. 320°C, λ_{max} (8.0) 267, 303 and 370 mμ; log ϵ_{max} 4.41; 4.29 and 4.45 resp. R_F 0.47 (A); 0.62 (B) and 0.71 (C); blue fluorescence. Yield: 13g (76%). (Found: C, 47.7; H, 3.5; N, 25.4; S, 22.9%. $C_{11}H_9N_5S_2$ requires: C, 48.0; H, 3.3; N, 25.45; S, 23.3.)

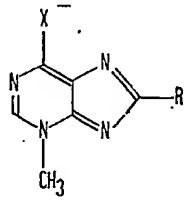
(c) preparation of 3 - methyl - 8 - (3'-pyridyl)purine

The dithioxanthine (11g) dissolved in conc. ammonia (400 ml) and DMF (50 ml) was stirred with Raney nickel (from 40g of alloy). After 90 minutes reflux, the solution was decanted from the catalyst and a second portion of Raney nickel added. After 2 hours reflux, the mixture was filtered and brought to dryness. The residue was treated with absolute ethanol. The crystals were dissolved in a small amount of water and the solution decolorised with sodium hyposulfite. Upon cooling, white hair-like needles of m.p. 220°C were obtained. λ_{max} (pH 8.0) 228, 311 mμ; log ϵ_{max} 4.24, 4.41; R_F (solvent C) 0.49; (solvent D) 0.45; grey-blue fluorescence (Found: C, 62.3; H, 4.4; N, 33.4%. $C_{11}H_9N_5$ requires C, 62.6; H, 4.3; N, 33.2.)

The di-picrate crystallised from water in blocks of m.p. 193°C. (Found: C, 41.4; H, 2.8; N, 23.5. $C_{23}H_{15}N_{11}O_{14}$ requires: C, 41.3; H, 2.2; N, 23.0.)

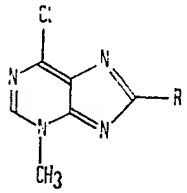
WHAT WE CLAIM IS:—

1. New 3-methylpurine derivatives of the general formula:



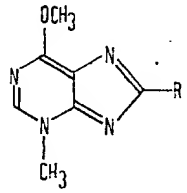
where R is hydrogen and X is chlorine, or a methoxy group; or R is an aromatic group or a heterocyclic group of aromatic character and X is hydrogen, or chlorine, or a methoxy group, or a methylamino group, or a dimethylamino group.

2. 3 - Methyl - 6 - chloropurines of the formula:



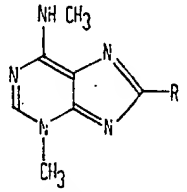
where R is hydrogen or an aromatic group or a heterocyclic group of aromatic character.

3. 3 - Methyl - 6 - methoxypurines of the formula:



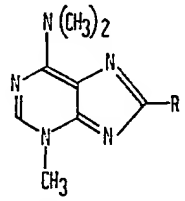
wherein R is hydrogen or an aromatic group or a heterocyclic group of aromatic character.

4. 3 - Methyl - 6 - methylaminopurines of the formula:



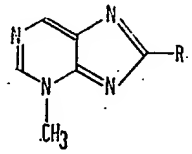
where R is an aromatic group or a heterocyclic group of aromatic character.

5. 3 - Methyl - 6 - dimethylaminopurines of the formula:



where R is an aromatic group or a heterocyclic group of aromatic character.

6. 3-Methylpurines of the formula:



where R is an aromatic group or a heterocyclic group of aromatic character.

7. 6-Chloro-3-methylpurine.

8. 6-Chloro-3-methyl-8-phenylpurine.

9. 6-Methoxy-3-methylpurine.

10. 6 - Methoxy - 3 - methyl - 8 - phenylpurine.

11. 6 - Dimethylamino - 3 - methyl - 8-phenylpurine.

12. 6 - Methylamino - 3 - methyl - 8-phenylpurine.

13. 3-Methyl-8-phenylpurine.

14. 3-Methyl-8-(3'-pyridyl)purine.

15. A method of preparing a 6 - chloro-3 - methylpurine as claimed in Claim 2, which comprises reacting the corresponding 3-methyl-6-methylthiopurine with gaseous chlorine in methanol solution at a temperature of below −3°C.

16. A method of preparing 6 - chloro - 3-methylpurines as claimed in Claim 2, substantially as hereinbefore described with reference to Example 1 and Example 5.

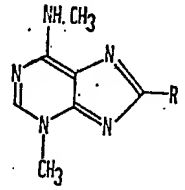
17. A method of preparing a 6 - methoxy-3 - methylpurine as claimed in Claim 3, which comprises reacting the corresponding 6-chloro-3-methylpurine with methanol at room temperature.

18. A method of preparing 6-methoxy-3-methylpurines as claimed in Claim 3, substantially as hereinbefore described with reference to Example 2 and Example 10.

19. A method of preparing a 6-methylamino-3-methylpurine as claimed in Claim 4, which comprises reacting the corresponding 3-methyl-6-methylthiopurine or the corresponding 6-chloro-3-methylpurine with monomethylamine.

20. A method of preparing a 6-methylamino-3-methylpurine as claimed in Claim 4, substantially as hereinbefore described with reference to Example 8.

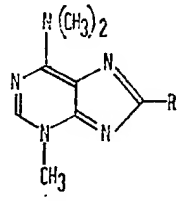
21. A method of preparing a 6-methylamino-3-methylpurine of the formula:



where R is hydrogen or an aromatic group or a heterocyclic group of aromatic character, which comprises reacting the corresponding 6-chloro-3-methylpurine with monomethylamine.

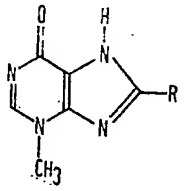
22. A method of preparing a 6-dimethylamino-3-methylpurine as claimed in Claim 5, which comprises reacting the corresponding 3-methyl-6-methylthiopurine or the corresponding 6 - chloro - 3 - methylpurine with dimethylamine.

23. A method of preparing a 6-dimethylamino-3-methylpurine of the formula:



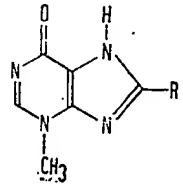
where R is hydrogen or an aromatic group or a heterocyclic group of aromatic character, substantially as hereinbefore described with reference to Example 3 or Example 9.

24. A method of preparing a 3-methylhypoxanthine of the formula:



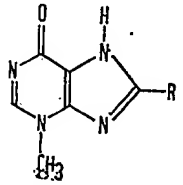
where R is hydrogen or an aromatic group or a heterocyclic group of aromatic character, which comprises heating the corresponding 6-chloro-3-methylpurine with sodium acetate in aqueous acetic acid.

25. A method of preparing a 3-methylhypoxanthine of the formula:



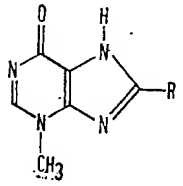
where R is hydrogen or an aromatic group or a heterocyclic group of aromatic character, from the corresponding 6-chloro-3-methylpurine, substantially as hereinbefore described with reference to Example 6.

26. A method of preparing a 3-methylhypoxanthine of the formula:



where R is hydrogen or an aromatic group or a heterocyclic group of aromatic character, which comprises reacting the corresponding 6 - methoxy - 3 - methylpurine with aqueous hydrochloric acid.

27. A method of preparing a 3-methylhypoxanthine of the formula:



where R is hydrogen or an aromatic group or a heterocyclic group of aromatic character, substantially as hereinbefore described with reference to Example 11.

28. A method of preparing 6 - thiono - 3-methyl - 8 - phenylpurine which comprises reacting 6 - chloro - 3 - methyl - 8 - phenylpurine with hydrogen sulphide in the presence of concentrated aqueous ammonia.

29. A method of preparing 6 - thiono - 3-methyl - 8 - phenylpurine substantially as hereinbefore described with reference to Example 7.

30. A method of preparing 3 - methyl - 8-phenylpurine which comprises reacting a suspension of 3 - methyl - 6 - methylthio - 8-phenylpurine in aqueous isopropanol with Raney nickel.

31. A method of preparing 3 - methyl - 8-phenylpurine substantially as hereinbefore described with reference to Example 4.

32. A method of preparing 3 - methyl - 8-(3′ - pyridyl)purine which comprises reacting a solution of 2,6 - dithio - 3 - methyl - 8-(3′ - pyridyl)purine in dimethylformamide and aqueous ammonia with Raney nickel.

33. A method of preparing 3 - methyl - 8-(3′ - pyridyl)purine substantially as hereinbefore described with reference to Example 12.

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